REMARKS

Claims 1-4, 12, 13, and 21-75 were pending when the Office action was issued. Caims 1-4, 12-13, 21-38, and 75 were rejected, whereas claims 39-74 (method claims) have been withdrawn from consideration by the Patent Office, and were not examined on the merits.

I. Support/Explanation for the Amendments

The amendment to page 14 corrects obvious typographical errors, and therefore does not introduce new matter. It renders moot the Examiner's objection in paragraph 5 of the action.

The binding limitation of claims 1 and 21 has been amended to specify binding to human VEGFR-3. Of course, peptides that bind human VEGFR-3 may also bind VEGFR-3 of other species.

The Markush groups of substitutable amino acids recited in claim 4 have been narrowed to remove some amino acids that are not among the preferred conservative substitutions in Tables I-III of the specification (and, in one instance, add two preferred conservative amino acid substitutions from the tables). Thus, these amendment find support in said tables.

The wording of multiple dependent claim language has been improved by making it more concise (without charging scope of meaning).

Claims 34 and 37 have been cancelled without prejudice to pursuing the subject matter of these claims in a related application.

New claim 76 depends from claims 1 and 21 and sets a size range of 8-25 residues for the claimed peptide. This claim finds support in the paragraph bridging pp. 14-15 (for example), which describes embodiments where the peptide is any length from 6-100 residues.

With any amendments filed in this application, the Applicants reserve the right to pursue original claims and originally claimed subject matter in subsequent prosecution, and/or in divisional or continuing applications.

II. The "New Matter" Rejection Under 35 U.S.C. §112 Should Be Withdrawn.

In paragraph 9 of the action, the Examiner alleged that the subject matter of claims 2 and 23 were amended in a manner that introduced new matter. Specifically, the Examiner alleged that the specification provided support only for peptides wherein cysteines were placed at the termini of an octapeptide. The Applicants respectfully traverse.

The Examiner's attention is directed to original claims 2 and 23, which recite the terminal cysteine limitation. It is improper to reject original claim language as "new matter."

The paragraph bridging pages 14-15 of the application, reproduced on page 2 of this submission, includes a description of peptides of lengths up to at least 100 amino acids, with terminal cysteines added:

> Preferred peptides are from 6 to 100 amino acids in length, e.g., 6, 7, 8, 9, 10, 11, 12, . . . 97, 98, 99, or 100 amino acids in length. Although peptide sequences are often described herein as linear sequences from the amino-terminus to the carboxy-terminus, it is contemplated that the peptides may be made cyclic by the formation of at least one bond between non-adjacent amino acids. For example, in one variation, the peptides are formed with terminal cysteines which can be made to form an intramolecular disulfide bond. Thus, in one preferred embodiment, the peptide further comprises amino- and carboxy- terminal cysteine residues.

The quoted paragraph continues by providing formulae for some preferred variations of the invention, stating, "For example, the peptide may comprise the amino acid sequence: $CX_1X_2X_3X_4X_5X_6XX_7X_8C$ (SEQ ID NO: 33), wherein $X_1X_2X_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 32) are defined as above, and C represents cysteine." However, the teaching of thes specific embodiments does not negate the more general teaching that peptides up to 100 amino acids, with terminal cysteines, are part of the invention.

In view of this support and other support in the application, the rejection should be withdrawn.

III. The Rejection Under 35 U.S.C. §112 (Written Description) Should Be Withdrawn

In paragraph 8, the Examiner rejected claims 1-4, 12-13, 21-38, and 75, alleging lack of written description. The Applicants respectfully traverse.

Although the text of the rejection is lengthy, it appears to be based on a few premises. First, the examiner asserts (p. 13), that the application discloses only a small group of specific peptides. This assertion is incorrect. The law does not evaluate written description based solely on an application's working examples. In fact, the law states that an application need not contain any examples *per se* to satisfy the written description requirement. The present application describes several genera of peptides, including peptides of 7-100 amino acids, and how to make such peptides (See application at pp. 14-41.) New claim 76 recites a narrower genus with a size range of only 8-25 amino acids.

Focusing on the genus of peptides defined by $X_1X_2X_3X_4X_5X_6X_7X_8$ in claim 1, it is clear that the claim scope is quite small in relation to many chemical and biomolecule claims routinely allowed by the Patent Office. Each of the eight positions in the formula in claim 1 is defined by a single amino acid residue, and the formula as a whole permits no more than three *conservative* amino acid substitutions relative to the specified amino acids. This genus defined by Applicants' core sequence and up to three conservative substitutions is, many orders of magnitude smaller than a typical polypeptide or polynucleotide genus defined, e.g., by a "95% identity" limitation relative to a much longer sequence. The written description training materials of the Patent Office explicitly approve of such claims, which embrace billions of potentially conservative or nonconservative variants. And according to the PTO's own Written Description Training Materials, such a 95% identity claim can be adequately described by a single disclosed embodiment. [1]

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[1] Example 14 of the US PTO Written Description Guidelines Training Materials (reproduced as Exhibit 1 in Applicant's response of October 20, 2004) describes a claim to a hypothetical genus of proteins claimed with the transition "having" and embracing a specific amino acid sequence and "variants" having a defined sequence similarity (at least 95%). In its analysis, the Patent Office explicitly observed that "the protein claimed may be larger than SEQ ID NO: 3" because the transition "'having' is open language, equivalent to 'comprising'," and concluded that the genus claim was adequately described, stating that "one of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus."

Second, the examiner asserts (p. 14) that there is "insufficient written description about the structure associated with function" of polypeptides of the invention that are 8-100 amino acids because "an isolated peptide without the amino acid sequence has no structure, much less binding to any VEGFR-3." The Patent Office says that, even assuming the $X_1X_2X_3X_4X_5X_6X_7X_8$ is adequately described, the rest of the 92 amino acids are not adequately described without the amino acid sequence. The flaw in this analysis is that the Patent Office is NOT properly basing its rejection on an evaluation of *structure associated with function*. Rather, the Patent Office is basing the rejection on the description of optional additional structure, *not required for function* and not required by the claims. The application demonstrates that short peptides, such as the peptide CGYWLTIWGC, can bind VEGFR-3. By teaching short peptide sequences and describing a genus of such sequences, the Applicants have fulfilled the written description requirement of providing structure generally, and structure associated with function specifically.[2] The application also describes how to make longer peptides that contain the core structure (the "necessary common attributes"), and assay them to confirm that they retain the binding function recited in the claims.[3] The application contemplates that the additional amino acids can be any amino acids.

Never has the Patent Office or its reviewing courts suggested that claims must be limited to exactly the features/structure associated with function. Quite to the contrary, the Patent Office grants, and reviewing courts routinely sustain, claims that use the open claim language "comprises/comprising" which, by definition, is permissive of additional elements that do not necessarily contribute to, or detract from, function. Because the written description requirement focuses on the "necessary common attributes" of what is claimed, there is no statutory requirement for describing or defining every additional element or variation that a person of ordinary skill could add to an invention that is described in the application and that is embraced by open claim language, such as "comprising" or "comprises." A basic search of the PTO's on-line patent collection, which spans only 30+ years of recent patents, reveals that more than 2.8 *million* patents have issued using the claim terms "comprises" or "comprising". All 2.8 million of these inventions (even the ones outside the field of biotechnology) theoretically

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2 See Footnote 1.

3 It is already well known that the natural ligands of VEGFR-3, including VEGF-C and VEGF-D, are longer than 100 amino acids.

embrace variations that include a potentially infinite number of amino acids of unspecified sequence! Focusing on the field of the invention, there are more than 50,000 issued U.S. patents with claims that include one or more of the terms "polypeptide comprising" OR "peptide comprising" OR "protein comprising" or variations thereof.[4] These, too, theoretically embrace embodiments with an infinite number of undefined additional amino acids, if one chooses to engage in the analysis of the current office action. As already explained, the current claim set is already much more limited than a typical "comprising" claim insofar as it sets a 100 amino acid limit to the length of the claimed peptide. New claim 76 recites an even smaller genus of 8-25 amino acid peptides. The law of written description does not concern itself with this academic exercise, but rather, focuses on whether the application demonstrates possession of the necessary common attributes of the invention.

Third, the rejection suggests a continued misinterpretation of the claims. Claim 1, for example, specifies that the peptide's amino acid sequence *consists of* 8-100 amino acids, and then further defines a core of eight residues that must be *included in the 8-100 amino acids* and that contributes to VEGFR-3 binding. The examiner's concern that there is no description of peptides longer than 100 amino acids is irrelevant to the current claim set. (Although claims 13 and 35 (amended) use the term "comprises/comprising", these claims depend from claims 1 or 21, and thus are properly interpreted to incorporate the 100 amino acid maximum recited in claim 1 or 21. See 35 U.S.C. §112, ¶4.)

Fourth, the Patent Office wrongly asserts that the description of cysteines used in the invention is limited to cysteines at the ends of the 8-mer formula. As explained in the preceding section, the description of the invention contemplates both embodiments. Original claims 2 and 25 also provide written description support for a terminal cysteine embodiment, because original claims form part of the written description.

Fifth, the Patent Office asserts that there is inadequate description of peptide structures that bind to VEGFR-3 forms other than human VEGFR-3. The amended claims specify that the peptides must bind to human VEGFR-3, rendering this issue moot.

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[4] Database query of ACLM/(((((("polypeptide comprising" OR "peptide comprising") OR "protein comprising") OR "polypeptide comprises") OR "peptide comprises") OR "protein

With respect to claims 30 and 32, the Examiner asserts that the fusion partner is inadequately described. These claims, too, find support in claims 30 and 32 as originally filed, as well as in the specification. This assertion is another example if failure to focus on whether the structure correlative with function is described. The analysis of these dependent claims should be analogous to generic claims found in Example 18 in the PTO's Written Description Training Materials. Example 18 involves a claim to a method of expressing a "protein of interest", wherein the novelty lies not in the protein per se, but in the method steps by which it is expressed. The training materials provide the guidance that, in such circumstances, a single embodiment of the "protein of interest" was enough to satisfy the written description requirement to support a completely generic claim reciting use of "a nucleic acid that encodes said protein of interest." In Example 18, a "particular nucleic acid is not essential to the claimed invention" because the novelty of the invention resided in the method of expression of the nucleic acid, not in its particular sequence. In the present case, like Example 18, a particular sequence for the fusion partner is not essential to written description of the invention as presently claimed, and novelty does not rest in a particular novel sequence of the fusion partner per se. Rather, adequate novelty lies in the VEGFR-3 binding peptide defined in the independent claims, and any combination of elements that includes such a peptide sequence should be deemed to be adequately described. The core binding structure is the "necessary common attribute" relevant to written description of this invention.

With respect to claim 33, the Examiner alleged that the only modification taught in the application for increasing *in vivo* circulating half life is an Fc fusion. This is incorrect. The application teaches, "Standard pharmaceutical and formulation chemistry is used to achieve such goals, e.g., through glycosylation, pegylation, introduction of non-hydrolyzable bonds, mixing with pharmaceutically acceptable diluents, adjuvants, or carriers, and the like." Additional description of half-life increasing modifications are found, e.g., at pages 32-34. Claim 33 represents yet another example of a dependent claim for which a brief description suffices in view of the skill of those in the art. The Examiner's concern that the claim encompasses any modification is misplaced, because the claim only encompasses modification that increase half-life, and would be interpreted in the context of the application.

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comprises"): yielded 54343 patents on November 19, 2006.

Claim 34 has been canceled without prejudice, rendering moot the rejection of that claim.

The *Eli Lilly* and *Rochester* cases cited by the Examiner are readily distinguishable on their facts. The former involved an attempt to claim a genus by name, without constraints on structure. The latter involved an attempt to claim wholly by function, without a single example. Neither set of facts has any relation to this case, which involves multiple examples and claims with structural limitations commensurate with the examples.

For all of these reasons, the rejection for lack of written description should be withdrawn.

IV. The Rejection Under 35 U.S.C. §112 (Enablement) Should Be Withdrawn

The Examiner maintains a rejection of claims 1-4, 12-13 and 21-38 and 75 under 35 U.S.C. §112, first paragraph, as allegedly not enabled by the description of the specification. The Examiner contends that Applicants have not taught how to make all isolated peptides comprising the claimed peptides (X_1-X_8, $GYWX_1X_2X_3W$, etc.) of 8-100 amino acids in length, and contends that there is insufficient guidance as to which larger peptides "comprising" the smaller peptide would maintain structure and function of binding to VEGFR-3. Applicants respectfully disagree.

At the outset, the Applicants reiterate and incorporate by reference arguments previously presented in their prior submissions because the arguments have been acknowledged, but not rebutted. The Applicants reiterate arguments in the preceding section relating to written description insofar as many of the issues raised by the Examiner in the two rejections are identical. The description of the invention, discussed in the preceding section, is an enabling description.

The Patent Office cites the Federal Circuit's *Wands* decision and cites the "*Wands* factors," and the Applicants agree that these principles govern a written description analysis. However, these principles continue to be misapplied.

Wands involved screening of large numbers of hybridomas to identify specific hybridomas that fell within the claim limitations. Because the patentee in *Wands* provided sufficient guidance to make and screen the hybridomas and presented working examples, that the enablement requirement was fulfilled. *In re Wands*, 858 F.2d 731, 740 (Fed. Cir. 1988). *In re Wands* does not hold that a specific number of working examples is required. In reaching a decision, the court in *Wands* considered that the inventor's disclosure provides considerable direction and guidance on how to practice the invention and presents working examples. *Id* at 740. This fact coupled with the high level of skill in the art renders the invention enabled in the courts' opinion. *Id*. Although a considerable amount of work may have been required to do the making and screening, such experimentation is routine, not "undue," according to *Wands*.

In the present application, the claims of the application are directed to a limited genus of peptides with specified amino acid length that bind to a specific cell receptor. The specification fully discloses methods to make the claimed peptides and methods to determine their binding specificity with respect to VEGFR-3. Similar to *Wands*, the invention provides a composition that binds to a specific binding target, with the binding identified using well-known screening methods. The present specification teaches methods to make the invention (e.g., peptide synthesis, phage display, other methods well-known in the art) and methods to screen the invention (e.g., VEGFR-3 binding assays), thereby providing ample guidance and direction to a worker of ordinary skill in the art. Also, the present specification provides several working examples, similar to the disclosure at issue in *Wands*. Moreover, the level of skill in the art of peptide synthesis and DNA manipulation is high.

Given the high level of skill in the art and the guidance provided by the Applicants to make and use peptides of the invention, a worker of ordinary skill would not be required to undertake undue experimentation to make or use the invention. The peptides of the invention require a specific sequence or limited (conservative substitution) variants within that sequence. Additionally, the peptide sequence is of a finite length, e.g., 100 or 25 amino acid maximum length, such that a limited number of peptides are available and the binding domain of the claimed peptide is short compared to other proteins or peptides. Therefore, making the peptide of the present invention and screening for activity are performed relatively quickly using routine techniques, and the total number of combinations is orders of magnitude smaller than where a large protein of complex structure is contemplated. The making and screening required by the

present invention (peptide synthesis) is much simpler and faster – more routine -- than the making and screening of hybromas and antibodies set forth in the facts of *In re Wands,* which the Court said was not undue experimentation. Experimentation, even if extensive, is not necessarily undue if it is routine in the art (*In re Wands*, 858 F.2d 731 (Fed. Cir. 1988)).

Notwithstanding these favorable considerations relative to *Wands*, and the fact that peptide synthesis and screening is much more routine than *Wand's* hybridoma synthesis, monoclonal production, and monoclonal screening, the Examiner for this case reaches the opposition conclusion from the conclusion drawn by the Federal Circuit in *Wands*. The Examiner acknowledges that actual working examples exist, and appears to say that only such examples are enabled. Notwithstanding the lip-service paid to *Wands*, the Examiner refuses to recognize that the application teaches methods for making peptides of varying lengths using techniques common in the art such as solid phase synthesis, preparation from a phage library, and recombinant expression systems, and teaches numerous assays, many *in vitro*, by which the peptides can be routinely screened. (See, e.g., page 42, line 1, to page 53, line 2.) The assays can be used to screen whole proteins (e.g., VEGF-C and VEGF-D) of significantly longer sequence than the peptides contemplated by the invention. The assay is not dependent on the size of the peptide and the working examples in the specification exemplify the assay, not limit it.

The claims are directed to a peptides of 8-100 amino acids or 8-25 amino acids, wherein the peptide includes a particular sequence of amino acids recited in the claims. The Examiner has failed to explain why well-known synthetic and recombinant techniques are not suitable for making substantially every polypeptide within the scope of the claims. Instead, the Examiner repeatedly expresses concern about the absence of a sequence for the (optional) additional amino acids for peptides longer than the required minimum ($X_1X_2X_3X_4X_5X_6X_7X_8$) sequence, up to 100 amino acids. The analysis under Section 112 and *Wands* really is much simpler. The common attribute necessary for receptor binding is a short peptide well-defined in the application, and the claims recite the structure of that peptide and embody a finite number of conservative substitution variants of that peptide. If the Examiner persists in the position that it would require undue experimentation to make and screen the 8-mer peptides having up to three conservative substitutions, as the claim specifies, the Applicants request an explanation of why screening the short peptides would be undue.

Because the sequence required for binding ($X_1X_2X_3X_4X_5X_6X_7X_8$ as defined in the claim) is specified in the claim, the enablement requirement is satisified for longer peptides as well. It entails only routine screening to add additional residues *of any sequence* to the core ($X_1X_2X_3X_4X_5X_6X_7X_8$) structure, and screen the resulting peptide to verify that the additional sequence did not interfere with the binding activity conferred by the core peptide. Because it is the core ($X_1X_2X_3X_4X_5X_6X_7X_8$) peptide that confers binding, the focus on the sequence of the additional residues is misplaced. For the purposes of enablement, the additional residues translate to routine screening, and nothing more.

In the current Office action the Examiner raises the issue of whether the application provides adequate guidance about the amino acid substitutions permitted by the claims, and cites a Mason reference which, the Examiner asserts, shows the unpredictability of substitutions. Mason has nothing whatsoever to do with the subject matter of the invention. The protein at issue is unrelated to the peptides of the invention, and the cysteine deletion-substitution performed by Mason is not relevant to claim 1, because $X_1X_2X_3X_4X_5X_6X_7X_8$ are not cysteines.

The Examiner also expressed concern about the unpredictability of whether VEGF-D polypeptides bind to VEGFR-2, citing a Baldwin reference. This concern, too, is misplaced, because the claims require binding to VEGFR-3, and the claims are not directed to VEGF-D.

Because Applicants have taught a worker of ordinary skill in the art to make and use the claimed peptides, with only routine screening experimentation, the rejection under 35 U.S.C. § 112, first paragraph, enablement, should be withdrawn.

VII. Conclusion

For the reasons given above, Applicants submit that the claims are in condition for allowance and request expedited notice of the same.

Respectfully submitted,

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